International Journal of Surgery 10 (2012) 187–189

Contents lists available at SciVerse ScienceDirect

International Journal of Surgery

journal homepage: www.theijs.com

Invited editorial

Pancreas cancer treatment: A surgeon's perspective today☆

In 1968 John Howard, one of the pioneers of pancreatic surgery, reported the first series of patients submitted to pancreatic resection without mortality. This contributed to reduce skepticism about pancreas surgery and to open a new surgical era. Nowadays, perioperative mortality after pancreaticoduodenectomy in high-volume centers does not exceed 2–3% of cases, and the goal of zero-mortality surgery has been reached by some centers.[1,2] These data have an outstanding value, since safe surgical resection remains the only potentially curative treatment for pancreas cancer.

In spite of this significant improvement in mortality rates, perioperative morbidity still remains a major problem, especially in patients undergoing pancreatic head resection. Even in high-volume centers, the perioperative morbidity rate after pancreaticoduodenectomy reaches 30% to 40%, without any trend toward reduction.[2] There is general agreement in the scientific community that this high rate is significantly correlated to the fact that the incidence of pancreatic fistula has not changed during the last ten years. Despite many technical proposals concerning pancreas remnant anastomosis and duct occlusion, and despite our better knowledge of factors influencing the onset of pancreatic fistula (small pancreatic duct, soft pancreas), we are still unable to reduce this serious complication. Perhaps there are factors that we do not yet understand, and new fields of investigation must be explored.

With regard to this aim, a recent clinical trial[3] shows that in highly selected patients, early drainage removal compared to late drainage removal is associated to a significantly lower rate of pancreatic fistula and abdominal complications. Thus, a prolonged period of drainage insertion seems to be an independent risk factor for pancreatic fistula in a selected group of patients. This interesting study is a clear demonstration that the surgeon still has work to do.

1. Pancreaticoduodenectomy: radical or palliative procedure? The growing importance of the pathological examination of resection margins

Approximately one-third of patients undergoing pancreaticoduodenectomy classified as "radical" (i.e. R0) develop local recurrence very soon after the operation. For many years this was considered to be the surgeon's fault, and so, in recent years, we have sought to improve our surgical technique, especially in performing retroduodenal margin (SMA margin) resection. Unfortunately, this was not enough.

Resection margin involvement (R1) is a key prognostic factor after pancreatic surgery,[4] but the R1 rate reported in the literature varies greatly, from 20% to 75%.[5,6]

Based on clinical data, there is a difference between rate of local recurrence and rate of resection margin involvement (R1). In fact, many centers report an incidence of local recurrence that is significantly higher than their rate of R1 resections. This remarkable difference limits the scope for meaningful comparison and precludes conclusions regarding the prognostic significance of resection margin status. But how can this discrepancy be explained? Resection margin involvement is generally believed to be determined by the quality of the surgery, with a lower R1 rate being considered an indicator of higher quality surgery. However, in recent years this concept has been criticized since studies have brought the pathologist as a second player onto the scene.

Due to anatomical considerations regarding the head of the pancreas (proximity of vessels and other organs), the resection margins of pancreaticoduodenectomy cannot, in some cases, be extended as would be necessary.

It is therefore evident that R1 rate is not necessarily a measure of the surgeon's performance, but it is almost always a measure of the performance of the pathologist. As a consequence it can be stated that there is a growing awareness that standardization and meticulousness of the pathological examination have a significant impact on the accuracy of the reported resection margin status.

In order to standardize the work of the pathologist a new method of pathological evaluation of the specimen after pancreaticoduodenectomy has been developed. This new method, first proposed by Verbeke,[7] takes into consideration the three spatial dimensions of the resected specimen, highlighting the importance, as in other organs, of the new concept of "circumferential margins". The different margins are identified by a multicolor system and the specimen is cut into several axial slices. In contrast to the generally adopted definition of R0 for pancreatic head cancer (tumoral tissue at 0 mm from the surgical margin), R0 is defined as a tumor-free margin of at least 1 mm.[7]

Several papers published in recent years have demonstrated that the use of this new standardized method to manage the specimen after pancreaticoduodenectomy leads to better staging and to a more accurate evaluation of R status. Adopting this new approach, R1 status is found in up to 80% of pancreas specimens.[7] As a consequence, we can assume that R0 resection for pancreas cancer is performed in only a minority of cases. If confirmed, this evidence will significantly impact the management of pancreatic cancer.

2. Vessel involvement: how far should we go?

Vessel involvement is present at diagnosis in one-third of cancers of the head or the body of the pancreas. To date, there is general agreement that venous involvement alone (portal vein

☆ This paper was not peer-reviewed.

1743-9191/$ – see front matter
doi:10.1016/j.ijsu.2012.03.004

and/or superior mesenteric vein) is not a contraindication to surgical resection, as is confirmed by data collected in a systematic review.[8,9] Patients with venous involvement submitted to vascular resection show good survival, and no increase in perioperative morbidity or mortality.[8]

On the contrary, tumor infiltration of the superior mesenteric artery or the celiac axis (encasement of more than 180°) must still be considered as unresectable disease. However, there is only limited data in the literature to support this statement.[10] Advances in pancreatic surgery, with significant improvement of patients' perioperative outcome, and in the absence of effective alternative therapeutic options, have therefore fueled an ongoing debate: are more radical surgical approaches allowed, in patients without metastases, in order to achieve tumor extirpation?

A large retrospective analysis,[11] and more recently a meta-analysis,[10] have been published on this topic. These papers provide evidence that pancreaticoduodenectomy with concomitant arterial resection is affected by poorer perioperative outcome and worse long-term survival if compared with pancreaticoduodenectomy alone or pancreaticoduodenectomy with venous resection. However, long-term survival following pancreaticoduodenectomy with arterial resection is superior to palliative treatment alone. The Authors conclude that arterial vascular resection should be undertaken only in highly selected patients, and should be performed only in high-volume centers.

3. Neoadjuvant treatment: is this the future?

Poor oncological outcome after "radical" surgery has, in recent years, increased the scientific community's attention to neoadjuvant treatment. Neoadjuvant treatment offers several advantages over up-front surgery. One of these is the identification of patients with occult metastatic disease, who would not benefit from surgical resection and could be spared the risks of an unnecessary operation.[12,13]

A second possible advantage is the reduction of microscopically positive margins after surgery.[14] Almost all patients who receive neoadjuvant therapies are able to complete treatment, whereas 25% of patients who undergo up-front surgery are unable to complete adjuvant therapy.

In evaluating these advantages of neoadjuvant treatment it is useful to divide patients into two groups: patients with initially resectable tumor, and patients with advanced tumor.

For patients with initially resectable tumors, the putative advantages of neoadjuvant therapy seem to be very promising. For this reason, recent consensus guidelines recommend that this approach should be put into common practice.[15] The logic is that neoadjuvant therapy will yield benefits for patients who progress during the treatment period by sparing them an unnecessary surgical intervention. A specific argument to support chemoradiation before surgery for patients with initially resectable tumors is that this therapy would achieve better local control of the disease, leading to a higher proportion of patients with R0 resection. However, since the definition of margin status is not consistent between different trials or different institutions, there is no clear evidence of this possible benefit.

A further hypothetical benefit of neoadjuvant treatment should be the achievement of better survival rates. Disappointingly, this hypothesis is not supported by data found in the literature.[16] Therefore, there is now general agreement that large randomized trials to compare up-front surgery with neoadjuvant therapy before surgery are warranted.

For patients with locally unresectable pancreatic cancer, potential tumor downsizing through chemoradiation promises to maximize the chance of a complete resection. However, the relatively low rate of resection after treatment in this set of patients requires very candid discussions with patients regarding the goal of therapy. In a recent meta-analysis,[17] only 39% of all patients after neoadjuvant treatment were surgically explored, but 72% of explored patients underwent a successful pancreatic resection. These data indicate two distinct anatomic sets among these patients: a responding group that may benefit from surgery, and a non-responding group for which preoperative therapy is largely ineffective. How can we explain this result? It can be consistently affirmed that the former group includes the vast majority of patients with "borderline resectable cancers," a distinct set whose management should be considered separately from resectable cancers and from those that are locally advanced. The largest study on patients with borderline resectable disease published to date, by the M.D. Anderson group,[18] demonstrates the good results of neoadjuvant treatment in this subset of patients.

In conclusion, pancreatic surgery has passed the test of time and is now a safe and effective treatment modality for patients affected by pancreatic cancer. However, pancreatic anastomotic fistula remains a major clinical problem requiring an evidence-based solution. A new method of pathological examination of the surgical specimen has shown that R1 rate after pancreaticoduodenectomy is significantly higher than that reported in the literature. It is now clear that at least 75% of our pancreaticoduodenectomies for cancer cannot actually be considered radical, due to the presence of cancer cells at the surgical margin. Surgical resection of patients with portal vein or mesenteric vein infiltration is an effective treatment modality, but only selected patients with arterial involvement would benefit from surgical resection. Finally, neoadjuvant treatment is the most promising therapeutic modality to improve long-term results of our patients. Ongoing trials will soon define this relevant topic.

Conflict of interest

None.

References

1. Cameron JL, et al. One thousand consecutive pancreaticoduodenectomies. *Ann Surg* 2006;**244**(1):10–5.
2. Aranha GV, et al. Zero mortality after 152 consecutive pancreaticoduodenectomies with pancreaticogastrostomy. *J Am Coll Surg* 2003;**197**(2):223–31. discussion 231–2.
3. Bassi C, et al. Early versus late drain removal after standard pancreatic resections: results of a prospective randomized trial. *Ann Surg* 2010 Aug;**252**(2):207–14.
4. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, et al. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997;**226**:248–60.
5. Verbeke CS, Leitch D, Menon KV, McMahon MJ, Guillou PJ, Anthoney A. Redefining the R1 resection in pancreatic cancer. *Br J Surg* 2006;**93**:1232–7.
6. Raut CP, Tseng JF, Sun CC, Wang H, Wolff RA, Crane CH, et al. Impact of resection status on pattern of failure and survival after pancreaticoduodenectomy for pancreatic adenocarcinoma. *Ann Surg* 2007;**246**:52–60.
7. Verbeke CS, et al. Redefining resection margin status in pancreatic cancer. *HPB* 2009;**11**:282–9.
8. Weitz J, Kienle P, Schmidt J, et al. Portal vein resection for advanced pancreatic head cancer. *J Am Coll Surg* 2007;**204**:712–6.
9. National Comprehensive Cancer Network (NCCN). *Guidelines in oncology: pancreatic adenocarcinoma*. Available at: http://www.nccn.org/professionals/physician_gls/PDF/pancreatic.pdf; 2008 [accessed 05.05.11].
10. Mollberg N, Rahbari NN, Koch M, Hartwig W, Hoeger Y, Buchler MW, et al. Arterial resection during pancreatectomy for pancreatic cancer: a systematic review and meta-analysis. *Ann Surg* 2011;**254**:882–93.
11. Boggi U, Del Chiaro M, Croce C, et al. Prognostic implications of tumor invasion or adhesion to peripancreatic vessels in resected pancreatic cancer. *Surgery* 2009;**146**:869–81.
12. Hoffman JP. Status of neoadjuvant therapy for resectable pancreatic cancer. *Surg Oncol Clin N Am* 2010;**19**:411–8.
13. Crane CH, Varadhachary G, Wolff RA, et al. The argument for pre-operative chemoradiation for localized, radiographically resectable pancreatic cancer. *Best Pract Res Clin Gastroenterol* 2006;**20**:365–82.

14. Cheng TY, Sheth K, White RR, et al. Effect of neoadjuvant chemoradiation on operative mortality and morbidity for pancreaticoduodenectomy. *Ann Surg Oncol* 2006;**13**:66–74.
15. Abrams RA, Lowry AM, O'Reilly EM, et al. Combined modality treatment of resectable and borderline resectable pancreas cancer: expert consensus statement. *Ann Surg Oncol* 2009;**16**:1751–6.
16. Gillen S, Schuster T, Meyer zum Büschenfelde C, et al. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. *PLoS Med* 2010;**7**: 1–15.
17. Andriulli A, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. *Ann Surg Oncol* 2011. doi:10.1245/s10434-011-2110-8.
18. Varadhachary GR, Tamm EP, Abbruzzese JL, Xiong HQ, Crane CH, Wang H, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. *Ann Surg Oncol* 2006;**13**:1035–46.

Roberto Coppola, MD, FACS, Professor of Surgery, Chairman
Department of Surgery,
Campus Bio Medico University School of Medicine, Rome, Italy
E-mail addresses: r.coppola@unicampus.it, robertocoppola@iol.it

Available online 16 March 2012